

## EDITORIAL COMMENT

# Evolving Strategies in the Treatment of Acute Myocardial Infarction in the Community Hospital Setting\*

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An ongoing challenge for the clinical cardiologist remains the choice of optimal reperfusion therapy for patients with ST-segment elevation acute myocardial infarction (STEMI) who present to community hospitals without on-site primary percutaneous coronary intervention (PCI). Numerous studies have demonstrated a clear superiority of primary PCI over pharmacologic thrombolysis for the treatment of STEMI, with higher initial reperfusion rates, improved event-free survival, and a lower incidence of intracranial bleeds (1,2). However, <25% of hospitals in the U.S. and <10% of centers in Europe have the capability of performing emergency PCI (3). As a result, referral of STEMI patients for PCI is usually associated with a significant time delay necessitated by the need for rapid transport to a tertiary center and the mobilization of appropriate resources.

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The importance of determining optimal reperfusion in the community hospital setting is underscored by the sheer number of involved patients and by recent data describing the timing of mechanical recanalization. Given the current practice of transporting patients to the nearest hospital for chest pain evaluation, over 50% of STEMI patients are initially evaluated in hospitals without on-site PCI capability (4). Despite the American College of Cardiology/American Heart Association (ACC/AHA)-recommended door-to-balloon times of  $90 \pm 30$  min (3), data on patients treated with PCI in the National Registry of Myocardial Infarction (NORMI) indicate a median treatment time delay of >2 h in 87% of patients transferred for mechanical intervention (5).

Several recent studies have continued to demonstrate improved clinical outcomes with primary PCI compared with pharmacologic reperfusion, even for patients who need to be transferred to a tertiary center for catheter-based therapy. In the Danish Multicentre Randomized Trial on Thrombolytic Treatment Versus Acute Coronary Angio-

plasty in Acute Myocardial Infarction (DANAMI-2) study, community STEMI patients transferred to a tertiary hospital for primary PCI had a lower composite incidence of death, recurrent infarction, or stroke at 30 days, compared with patients receiving on-site thrombolytic therapy (8.5% vs. 14.2%,  $p = 0.002$ ) (6). Similarly, in the Primary Angioplasty in Patients Transferred From General Community Hospitals to Specialised PTCA Units With or Without Emergency Thrombolysis (PRAGUE) study, there was an 8% rate of death, myocardial infarction (MI), or stroke at 30 days in community hospital patients transferred for primary PCI, compared with 23% for on-site thrombolysis alone and 15% for patients treated with both thrombolysis and primary PCI ( $p < 0.02$ ) (7). Finally, in the Air Primary Angioplasty in Myocardial Infarction (AIR-PAMI) study, there was a 38% reduction in the 30-day composite incidence of death, MI, or stroke in patients emergently transferred for PCI versus on-site thrombolysis (8.4% vs. 13.6%,  $p = 0.331$ ). Although this difference in outcome was not significant, a secondary, prespecified analysis using step-down, multivariate, logistic regression demonstrated that the strategy of transfer for primary PCI was independently associated with a reduction in the primary end point (odds ratio 0.159,  $p = 0.028$ ) (8).

Despite the continued superiority of mechanical intervention even in the setting of interhospital transfer, it is clear that a prolonged delay in achieving reperfusion in the infarct vessel has deleterious results. Ample data drawn from multiple fibrinolytic studies have previously demonstrated that the time from symptom onset to infarct vessel recanalization is an important independent predictor of myocardial salvage and survival (9–11). Although the limited number of STEMI patients studied in PCI trials has hindered a similar assessment of the impact of reperfusion timing, a recent analysis of 27,000 PCI patients in the NORMI registry demonstrated that a door-to-balloon time >2 h was associated with a 41% to 62% increase in mortality, compared with patients with shorter intervention times (4).

Another important concept concerning the efficacy of PCI for STEMI is the observed clinical benefit of achieving Thrombolysis In Myocardial Infarction (TIMI) flow grade 3 in the infarct vessel before mechanical intervention. In a recent study combining data on over 2,500 patients from four PAMI trials, clinical outcomes were compared in patients who had achieved TIMI flow grade 3 spontaneously before PCI with patients who presented with TIMI flow grade 0, 1, or 2. Consistent with data on the impact of reperfusion times, patients with spontaneous pre-PCI TIMI flow grade 3 had a lower mortality, improved left ventricular function, and lower rates of congestive heart failure. However, patients with TIMI flow grade 3 also had higher procedural success rates, with higher rates of TIMI flow 3 after the intervention. The authors theorized that improved procedural outcomes may have resulted from decreased thrombotic burden at the intervention site, less

\*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of JACC or the American College of Cardiology.

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distal microvascular embolization, and improved lesion delineation (12).

Given the need to minimize the time of reperfusion and the paramount importance of TIMI flow grade 3, there have been several new strategies proposed to improve outcomes for STEMI patients presenting to the community hospital. One approach has been to expand PCI capability to acute-care centers without on-site cardiac surgery backup, thereby avoiding the inherent time delay associated with interhospital transport. Publication of data from the Atlantic Cardiovascular Patient Outcomes Research Team (C-PORT) trial has fostered the current opinion that there should be increased dissemination of PCI capability at community hospitals (13). Several investigators have suggested that all STEMI patients should be treated as “trauma victims,” with immediate transport only to “cardiac trauma centers” that offer PCI.

An alternative approach to the increased establishment of PCI programs has been the resurgent use of “facilitated PCI” (14). Facilitated PCI involves the adjunctive use of pharmacotherapy used in combination with mechanical revascularization to achieve early, complete, and sustained flow in the infarct-related epicardial artery and in the infarct-zone microvasculature. Given the universal availability of pharmacotherapy, the desired goal of facilitated PCI is to improve STEMI outcomes by rapidly administering drugs in the community hospital and during interhospital transfer in an attempt to induce earlier infarct-vessel and tissue-level reperfusion while awaiting definitive intervention in the catheterization laboratory. This complementary approach theoretically combines the strengths of pharmacologic and mechanical revascularization, thus shortening the time to TIMI flow grade 3, providing a better substrate for PCI, and widening the therapeutic window for beneficial revascularization. Potential adjunctive drugs that may have a role in facilitated PCI include full- or partial-dose thrombolytics, glycoprotein (GP) IIb/IIIa inhibitors, low-molecular-weight heparins, direct thrombin inhibitors, and thienopyridines.

Despite theoretic considerations that optimal reperfusion might be achieved with complementary pharmacologic and mechanical approaches, early attempts to combine these therapies in the STEMI setting were disappointing. The earliest “facilitated PCI” trials involved combined use of thrombolytics with balloon angioplasty. Data from the Thrombolysis and Angioplasty in Myocardial Infarction (TAMI-1) study, the TIMI-IIa study, and the European Cooperative Study Group trial all demonstrated that routine immediate intervention with balloon angioplasty in the setting of thrombolytic therapy conferred no benefit with respect to survival or ventricular function and was in fact associated with higher complications (15–17).

The debate concerning the merits of combined pharmacologic and mechanical therapy has been clearly altered by improvements in fibrinolytic agents, adjunctive antiplatelet and antithrombin pharmacology, and the refinement of

catheter-based techniques. The development of “bolus thrombolytics” has provided new a new class of agents with enhanced fibrin sensitivity, excellent safety and efficacy profiles, and greater ease of administration, potentially shortening the time between symptom onset and treatment (18). Similarly, the combined use of thrombolytics (including reduced or half dose) with GP IIb/IIIa inhibitors has been theorized to engender more stable reperfusion by potentiating fibrinolysis with platelet disaggregation. Data from the Global Use of Strategies to Open Occluded Coronary Arteries V (GUSTO V) (19) and Assessment of the Safety and Efficacy of a New Thrombolytic Regimens (ASSENT-3) (20) trials have demonstrated that the speed and quality of infarct-vessel reperfusion may be increased with this strategy, with a reduced incidence of recurrent ischemic events, including in-hospital re-infarction, recurrent or refractory ischemia, or urgent PCI. Other agents that may theoretically provide for more comprehensive clot lysis with more rapid, complete, and sustained myocardial perfusion include low-molecular-weight heparins, direct thrombin inhibitors, and thienopyridines.

Improvements in pharmacologic reperfusion have been paralleled by simultaneous refinement of mechanical revascularization techniques. Apart from increased operator experience, advances in catheter design, refinement of heparin dosing regimens in the catheterization laboratory, and the development of arteriotomy closure devices, intracoronary stenting has been shown to be superior to balloon angioplasty in STEMI patient with less recurrent ischemia, less early re-occlusion, and reduced late infarct-vessel restenosis (21). Mechanical thrombectomy and distal embolization protection devices are two additional modalities that are currently being tested and may have a role in the treatment of STEMI patients.

A critical question which remains is whether the advancements that have occurred separately with pharmacologic or mechanical reperfusion will result in improvements in safety and efficacy with the combined use of these therapies. In the Plasminogen-activator Angioplasty Compatibility Trial (PACT), STEMI patients treated with combined reduced-dose tissue-type plasminogen activator (t-PA) and immediate catheterization with angioplasty, as indicated, had higher pre-PCI rates of TIMI flow grade 3 in the infarct vessel compared with patients treated with mechanical revascularization alone, with no adverse effects of combined therapy (22). Similarly, in the Strategies for Patency Enhancement in the Emergency Department (SPEED) trial, the combined use of reduced-dose reteplase, abciximab, and urgent catheterization with PCI was not associated with any increased risk and resulted in the highest rates of TIMI flow grade 3 on initial angiography, as compared with other treatment regimens (23). In a more recent study re-evaluating 1,938 patients from the TIMI-10B and TIMI-14 trials, the combined use of thrombolysis (with and without abciximab) with rescue, adjunctive, or delayed PCI resulted in a lower 30-day composite of death and re-

infarction, compared with patients with "successful thrombolysis" who did not undergo revascularization (24). Finally, in the Abciximab Before Direct Angioplasty and Stenting in Myocardial Infarction Regarding Acute and Long-Term Follow-up (ADMIRAL) trial, the combined use of primary stenting with abciximab versus stenting with placebo resulted in significant reductions in the composite end point of death, re-infarction, and urgent target vessel revascularization at both 30 days and 6 months (25).

As another study demonstrating a possible role for facilitated PCI, Scheller et al. (26) have presented results of the South West German Interventional Study in Acute Myocardial Infarction (SIAM III) trial in this issue of the *Journal*. Following full-dose thrombolytic therapy, 163 STEMI patients from the community hospital were randomized to either a strategy of transport to a tertiary center for immediate stenting or delayed stenting two weeks later. The immediate stenting strategy resulted in a significant reduction in the six-month combined end point of ischemic events, death, re-infarction, and target lesion revascularization (25.6% vs. 50.6%,  $p = 0.001$ ). This beneficial effect was mainly driven by a reduction in recurrent ischemic events in the immediate stenting group (4.9% vs. 28.4%,  $p = 0.01$ ). On an intention-to-treat basis, immediate stenting was also associated with a reduction in the six-month combined end point of death, re-infarction, and target lesion revascularization (27.7% vs. 39.8%,  $p = 0.049$ ). In addition, immediate stenting was associated with improved left ventricular ejection fraction at two weeks, as well as a further improvement in the ejection fraction at six months.

As a "real-world" reperfusion trial, SIAM III illustrates many of the problems commonly observed in treating STEMI patients from the community hospital. The mean 3.2 to 3.6 h "time to thrombolysis" and the mean 6.7 h "time to angiography" in the immediate stenting group exceed the optimal door-to-needle and door-to-balloon times currently recommended. The use of full-dose thrombolytic therapy without immediate PCI in the delayed stenting group was associated with an unacceptable 30-day 24.7% incidence of recurrent ischemic events, a 30-day 12.3% incidence of death or re-infarction, and a two-week 58.9% incidence of TIMI flow grade 3 in the infarct vessel. Similarly, the use of full-dose fibrinolytic therapy in both study arms was associated with an unacceptably high 8.6% incidence of major bleeding, including a 2.4% incidence of stroke. Other limitations of the study include the relatively low use of GP IIb/IIIa inhibitors, the use of full-dose thrombolytic therapy in the setting of cardiogenic shock, and a small, underpowered study size.

Apart from these limitations, however, the SIAM III study does rekindle ongoing interest in the facilitated PCI concept. Over 60% of patients in the immediate stenting group had baseline TIMI flow grade 3 in the infarct vessel at the time of initial angiography, with a 97.5% incidence of TIMI flow 3 following the intervention and a 98.6% incidence at two weeks. Patients in both groups with TIMI

flow grade 2 or 3 before the intervention had improved ventricular function at two weeks and six months, compared with patients with TIMI flow grade 0 or 1. Finally, despite relatively long treatment times, the combined use of full-dose thrombolytics with transfer for immediate stenting resulted in a relatively low 4.9% incidence of death and a 7.3% incidence of death or re-infarction at 30 days.

It is clear that more data are needed to determine the efficacy and safety of the facilitated PCI approach. A true assessment of this strategy will await the results of ongoing clinical trials, including among others FINESSE (Facilitated Intervention with Enhanced Reperfusion Speed to Stop Events), ADVANCE-MI (Addressing the Value of Facilitated Angioplasty After Combination Treatment or Eptifibatide Monotherapy in Acute Myocardial Infarction), and ASSENT-4 PCI. Additional studies will be needed to fully evaluate the ever-increasing armamentarium of pharmacologic agents and ongoing improvements in mechanical revascularization. The obvious goal of all of these efforts is to end the long-standing debate about the relative superiority of pharmacologic over mechanical intervention, so that we can move forward in an attempt to find an even better reperfusion option. Such an approach is clearly needed for all patients, but particularly for the STEMI patient presenting to the community hospital without immediate access to a catheter-based therapy.

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